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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,664	08/17/2001	Denise L. Faustman	DLF-002.1P	4530

7590 02/11/2003
Leon R Yankwich
Yankwich & Associates
201 BROADWAY
Cambridge, MA 02139

EXAMINER

AFREMOVA, VERA

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 02/11/2003

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/913,664

Applicant(s)
Faustman

Examiner
Vera Afremova

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1651



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Nov 19, 2002
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-37 is/are pending in the application.
- 4a) Of the above, claim(s) 15-37 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3 6) ☐ Other:

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DETAILED ACTION

Claims 1-37 are pending.

Election/Restriction

Applicant's election with traverse of Group I invention (claims 1-14) in Paper No. 8 filed 11/19/2002 is acknowledged. The traversal is on the grounds that the pending claims do not represent distinct inventions and/or serious burden in searching and examining (response page 3, last par.). This is not found persuasive because under PCT Rule 13.1 and PCT Rule 13.2 the claimed inventions do not relate to a single general inventive concept and they lack the same or corresponding special technical feature or a contribution each of the claimed inventions, considered as a whole, makes over the prior art. The donor tissues treated with enzymes in order to remove MHC class I antigens and to render suitable for transplantations, are known in the art as adequately demonstrated by US 6,110,206 which was cited in the prior office action (col. 8, lines 65-67). Applicants appear to argue that the final enzyme treated transplant product of the cited patent comprises dead cells (response page 3, par. 2). However, the enzyme application as taught by US 6,110,206 (col.7, lines 5-15 and lines 28-30) is not a lethal treatment of transplant tissues but rather a removal of the immune response related epitopes from the donor transplant tissues in order to render them non-immunogenic and suitable for transplantation as encompassed by the presently claimed method drawn to inhibiting rejection and/or inhibiting recipient immune response after transplantation. Moreover, as to the question of burden of search, the literature search, particularly relevant in this art, is not co-extensive and is much more important in

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evaluating the burden of search. Burden in examining materially different groups having materially different issues also exists. Clearly different searches and issues are involved with donor tissue transplant products, method of preparing the products and methods of inhibiting donor tissue transplant rejection. For these reasons, the restriction requirement is deemed proper. The restriction requirement is hereby made FINAL.

Claims 15-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Claims 1-14 are under examination in the instant office action.

Claim Rejections - 35 USC § 112

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 12 are rendered indefinite by the phrase “temporarily ablating MHC class I antigens” in the lack of proper definitions. It is uncertain what is “temporarily” and for how long this period is intended in the claimed method for inhibiting rejection. The as-filed specification does not provides definitions for the “temporarily” term except some vague interpretation that the tissue is, at least temporarily, rendered resistant to immune-mediated attack by the host’s immune system (page 1, line 12).

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Claim 12 is indefinite with regard to “a period of time sufficient for MHC class I antigens to regenerate” because it is uncertain as claimed and as disclosed how long is the “sufficient” period and/or what are protocols or criteria to establish when antigens are regenerated in the claimed method for inhibiting rejection. Further, it is not clear as claimed when the second transplanting step takes place in the claimed method. Does it take place after the “sufficient” period or regardless the “sufficient” period?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 5-8 are rejected under 35 U.S.C. 102(b) as being anticipated by US

4,399,123 [IDS-AB].

Claims are directed to a method for inhibiting rejection by a host mammal of another mammal donor tissue wherein the method comprises step of treating a mammal donor tissue with an enzyme effective for removing MHC Class I antigen and step of transplanting the treated tissue into a host mammal. Some claims are further drawn to donor and host mammals belonging to the same species or to the different species. Some claims are further drawn to the use of tissues such as skin cells. Some claims are further drawn to the use of a second enzyme to remove antigenic surface structure from the donor tissue.

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US 4,399,123 discloses a method for inhibiting rejection of donor tissue (example 1) wherein the method comprises step of treating a mammalian donor tissue with first proteolytic enzyme (col. 6, line 52) and second carbohydrate splitting enzyme (col. 6, line 53) in order to remove antigenic structures including antigenic glycoproteins and polysaccharides (col. 2, line 15) and transplanting the enzyme treated donor tissue into another mammal host (col.6, line 57). The particular enzymes are trypsin or chymotrypsin and amylase (examples 1-4). The suitable proteolytic enzymes include papain (col. 2, lines 63-64). The transplant tissues are human or animal dermis, tendon an ligament tissues (examples 1-4). The cited patent teaches that the enzyme treated donor tissues including human or animal tissues are suitable for both homo- and hetero-transplantations in the method for inhibiting transplant rejection and ablating recipient immune response (col. 2, lines 1-45 or example 1).

The cited patent US 4,399,123 is considered to anticipate the claimed invention because it teaches identical method for inhibiting transplant rejection comprising identical active steps of treating and transplanting donor tissues and identical structural elements including two enzymatic treatments and various combinations of donor tissues and host organisms as the claimed method. Although the cited patent does not clearly point out the removal of MHC Class I antigenic molecules, it teaches an enzyme treatment of donor tissue for the same purpose of removal of antigenic groups or molecules. Therefore, the cited method is reasonably expected to result in the removal of glycoproteins such as MHC Class I molecules particularly in view that two identical types of enzymes such as proteolytic and carbohydrate splitting enzymes are used for removal of

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antigenic structures including glycoproteins (col. 2, line 16). Moreover, the cited patent teaches that after transplantation into the host mammal of the enzyme treated donor tissue there were no evidence of lymphocytes infiltration (col. 6, line 61) and, thus, the treated transplant tissue was, at least "temporarily", rendered resistant to immune-mediated attack by the host's immune system within the scope of the presently claimed invention.

Claims 1-3, 5-7, 9 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,397,353 [A].

Claims are directed to a method for inhibiting rejection by a host mammal of a donor tissue transplant derived from another mammal wherein the method comprises step of treating a mammal donor tissue with an enzyme effective for removing MHC Class I antigen such as papain and step of transplanting the treated tissue into a host mammal. Some claims are further drawn to donor and host mammals belonging to the same or to the different species. Some claims are further drawn to the use of tissues such as skin or skin cells. Some claims are further drawn to the second transplanting step in the method for inhibiting transplant rejection.

US 5,397,353 [A] discloses a method for inhibiting rejection by a host mammal of a donor tissue transplant derived from another mammal wherein the method comprises step of treating a mammal donor tissue with an enzyme effective for removing MHC Class I antigen such as papain (col. 6, line 20), step of transplanting the treated tissue into a host mammal (col. 6, line 30) and second transplanting step (col. 6, line 40-41). The method of the cited patent is applied to mammals belonging to the same and/or to the different species including pigs and rats

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in a particular example (col. 6, line 14, 30 and 41). The transplantation of the enzyme treated tissues result in elicitation of immunological reaction (col. 6, line 34; col.5, line 14). The cited patent teaches applicability of the method of inhibiting transplant rejection for both human and animal tissues for both homo-and hetero-transplantations (col. 3, lines 26-28). It also encompasses optional treatment with second type of enzyme or with a carbohydrate-splitting enzyme effective for removal of antigenic moieties of polysaccharide nature (col. 4, lines 65-68).

The cited patent US 5,397,353 is considered to anticipate the claimed invention because it teaches an identical method for inhibiting transplant rejection comprising identical active steps of papain enzymatic treatment of donor tissues and two steps of transplanting. Although the cited patent does not clearly point out that the papain treatment results in the removal of MHC Class I antigenic molecules, it teaches the use of enzymatic treatment including papain treatment for the same purpose as the presently claimed invention such as removal of antigenic groups or molecules and inhibiting immune response in transplant recipient. Therefore, the cited method is reasonably believed to result in the removal of the same glycoproteins including MHC Class I molecules particularly in view that the identical papain enzyme is applied to the donor tissues and in view that the immunological reactions were absent or elicited after transplantation of papain treated donor tissue. Thus, the method for inhibiting transplant rejection of the cited patent results in ablating, at least temporarily, of the immune-mediated attack by the host's immune system within the scope of the presently claimed invention.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-9 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,399,123 [IDS-AB] and US 5,397,353 [A] taken with Galati et al. [IDS-AR].

Claims are directed to a method for inhibiting rejection by a host mammal of a donor tissue transplant derived from another mammal wherein the method comprises step of treating a mammal donor tissue with an enzyme effective for removing MHC Class I antigen and step of transplanting the treated tissue into a host mammal. Some claims are further drawn to donor and host mammals belonging to the same or different species. Some claims are further drawn to host mammal being human. Some claims are further drawn to the use of tissues cells and/or organs including skin, blood and/or lymphocytes. Some claims are further drawn to the second transplanting step in the method for inhibiting transplant rejection.

The cited patents 4,399,123 [IDS-AB] and US 5,397,353 [A] are relied upon as explained above for the disclosure of methods for inhibiting transplant rejection wherein the method comprises steps of treating a mammal donor tissue with enzymes effective for removal of antigenic molecules including antigenic glycoproteins and polysaccharides and step of transplanting the treated tissue into host mammal. The particular enzyme which is employed for

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the removal of antigenic moieties is papain in the method of US 5,397,353. The cited patent US 4,399,123 teaches the equivalency of proteolytic enzymes including trypsin and papain in the method for inhibiting transplant rejection. The exemplified method of the cited US 4,399,123 comprises one transplanting step. But the exemplified method for inhibiting transplant rejection of the cited US 5,397,353 comprises two transplanting steps. Both cited patents teach and suggest donor tissue enzymatic treatment with two types of enzymes in the methods for inhibiting transplant rejection as explained above. Both cited patents teach and suggest applicability of the disclosed methods for both human and animal donor tissues and for both homo-and hetero-transplants as explained above.

Although the cited patents US 4,399,123 [IDS-AB] and US 5,397,353 [A] do not clearly point out that the enzymatic treatment with proteolytic enzymes including papain is responsible primary for the removal of MHC Class I antigenic molecules in the method for inhibiting transplant rejection, they either clearly teach {US 5,397,353} or suggest {US 4,399,123} the use of a papain treatment of donor tissue transplants in the methods for inhibiting transplant rejection. The cited patents also clearly teach the necessity of removal of antigenic glycoproteins for inhibiting transplant rejection.

In addition, the reference by Galati et al. [IDS-AR] clearly particularly demonstrates that papain removes MHC Class I molecules of glycoprotein nature from cell surface (abstract) and it teaches that the MHC class I glycoproteins are expressed on nearly all nucleated cells (page 77, col. 1, par. 2). It also teaches that other than the MHC class I surface associated molecules

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remain unaffected by papain digestion (page 79, col. 1, last par.). In particular, the reference by Galati et al discloses treatment of blood cells or lymphocytes with papain for removal of the MHC class I antigens.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use papain for removal of MHC class I antigens in the method for inhibiting transplant rejection with a reasonable expectation of success in at least temporarily ablating immune response of transplant recipient as taught and/or suggested by the cited patents US 4,399,123 [IDS-AB] and US 5,397,353 [A] because papain tissue treatment results in disappearance of MHC class I glycoprotein antigens from surface membrane of all cells and/or tissues while in affecting other surface membrane associated molecules as clearly taught by Galati et al. [IDS-AR]. The use of human and/or animal donor tissues for homo- and hetero-transplants would have been obvious to one having ordinary skill in the art at the time the claimed invention was made as clearly suggested by both cited patents US 4,399,123 [IDS-AB] and US 5,397,353 [A]. Further, incorporation of second transplanting step in the method for inhibiting transplant rejection is considered to be within the purview of one having ordinary skill in the art of surgery depending on a particular surgery design and/or transplantation needs of a particular host mammal. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

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Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,399,123 [IDS-AB] and US 5,397,353 [A] taken with Galati et al. [IDS-AR] as applied to claims 1-9 and 12-14 above, and further in view of Stone et al. [IDS-BJ].

Claims 1-9 and 12-14 as explained above. Claim 10 is further drawn to the second enzyme being galactosidase in the method for inhibiting transplant rejection. Claims 11 is further drawn to the use of two particular enzymes such as papain and galactosidase together in the method for inhibiting transplant rejection.

The cited references US 4,399,123 [IDS-AB] and US 5,397,353 [A] taken with Galati et al. [IDS-AR] are applied as explained above for the teaching of a method for inhibiting transplant rejection comprising treating the donor tissue with two type of enzymes such as a proteolytic including papain for removal of the MHC class I antigens of glycoprotein natures {US 4,399,123 [IDS-AB] and US 5,397,353 [A] taken with Galati et al. [IDS-AR]} and carbohydrate-splitting enzyme for removal of antigens of polysaccharide nature {US 4,399,123 [IDS-AB] and US 5,397,353 [A]}.

Although the cited patents US 4,399,123 [IDS-AB] and US 5,397,353 [A] teach the use of second carbohydrate-splitting enzyme for removal of antigens of polysaccharide nature they are missing disclosure about galactosidase.

But the reference by Stone et al. [IDS-BJ] discloses a method for inhibiting transplant wherein the method comprises step of treating donor tissue with galactosidase and step of transplanting the treated tissue in to host recipient and wherein the method results in a reduction

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of inflammatory reaction or immune response of recipient host (pages 1577-1578 at paragraphs "Methods" and "Conclusions").

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use galactosidase of the reference by Stone as a carbohydrate-splitting enzyme in the methods for inhibiting transplant rejection of US 4,399,123 [IDS-AB] and/or US 5,397,353 [A] with a reasonable expectation of success in removal of antigenic molecules having polysaccharide nature because tissue treatment with galactosidase results in the removal of carbohydrate-containing antigenic epitopes and in the reduction of host immune reaction as taught by Stone et al. [IDS-BJ]. One of skill in the art would have been motivated to use a combination of a proteolytic enzyme including papain and a carbohydrate-splitting enzyme including galactosidase for the removal of both types of antigens including MHC class I antigens of glycoprotein nature and antigens of carbohydrate or polysaccharide nature for the expected benefit in the reduction and/or inhibiting immune response of the donor tissue recipient as adequately demonstrated by all the cited references. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova

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February 7, 2003.

VERA AFREMOVA

PATENT EXAMINER

A handwritten signature in cursive script, appearing to read "V. Afremova", followed by a horizontal line.